99 Aminotransferases

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Definition

Aminotransferases or transaminases are a group of enzymes that catalyze the interconversion of amino acids and oxoacids by transfer of amino groups. Aspartate aminotransferase (AST), formerly termed glutamate oxaloacetate transaminase (GOT), and alanine aminotransferase (ALT), formerly termed glutamate pyruvate transaminase (GPT), are the two aminotransferases of greatest clinical significance. Pyridoxal-5′-phosphate (P5′P) functions as coenzyme in the amino transfer reactions. In all amino transfer reactions, 2-oxoglutarate and L-glutamate serve as one amino group acceptor and donor pair.

$$\text{L-Amino acid} + \text{2-oxoglutarate} \longleftrightarrow \text{2-Oxoacid} + \text{L-glutamic acid}$$

The specificity of individual enzymes determines the specific amino acid that serves as the other amino group donor. In the AST reaction, the L-amino acid is aspartate; for ALT, it is alanine. The reactions are shown on the facing page.

Technique

The transaminase reaction cannot be directly monitored; however, continuous monitoring assays can be achieved by coupling to self-indicating enzyme systems that utilize as substrate either glutamate or the specific oxoacid formed in the transaminase reaction. Kinetic assays utilizing coupled enzyme systems are most commonly used in clinical laboratories. Older methods using colorimetric detection of transaminase reaction products without continuous reaction monitoring are obsolete. Proposed reference methods also recommend addition of pyridoxal phosphate to the reagent system in order to activate all of the enzyme. However, this modification introduces technical problems, compromises established clinical experience, and has not been uniformly adapted. Reagent addition of the coenzyme increases enzyme activity by 50% for AST in normal serum and by 20% for AST. Greater changes may occur in patient serum with low levels of pyridoxal phosphate caused by precursor vitamin B_6 deficiency.

Serum is the specimen of choice. In vitro hemolysis causes spuriously increased activity because of enrichment by erythrocyte aminotransaminase. Heparinized, EDTA, citrated, or oxalated plasma are generally acceptable but may cause problems with specific reagent-instrument systems. Serum transaminase activity is stable at room temperature for several hours or up to 3 days at 4°C. Freezing may result in loss of activity and is not recommended.

Basic Science

Aminotransferases catalyze the redistribution of nitrogen between amino acids and corresponding oxoacids participating in both protein metabolism and gluconeogenesis. They are ubiquitous in their cellular distribution.

Tissue activity for AST is as follows in decreasing concentration: heart, liver, skeletal muscle, kidney, pancreas, spleen, lung, and erythrocyte. Two distinct forms have been identified: a cytoplasmic, or soluble isoenzyme, and a mitochondrial isoform. Selective measurement of these isoenzymes has no currently demonstrated clinical application.

The distribution and relative tissue concentration of ALT is similar but importantly different. Highest activity is found in the liver, followed by kidney, myocardium, skeletal muscle, pancreas, spleen, lung, and erythrocyte. ALT activity is found in the cytosol; organ- or organelle-specific isoenzymes have not been demonstrated. The concentration of ALT in hepatic cell cytoplasm is comparable to AST; however, a mitochondrial ALT isoform is not found. In all other tissues, ALT activity is significantly less than AST.

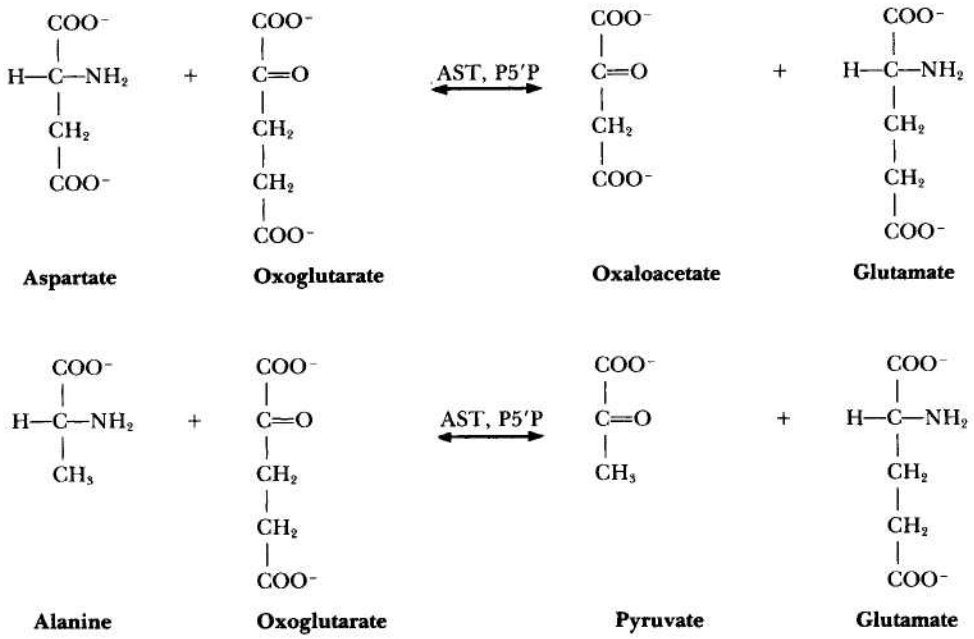
Clinical Significance

The primary clinical application of serum AST and ALT measurement is the detection and differential etiologic diagnosis of hepatic disease. Hepatic cell injury is manifested by elevated serum transaminase activity prior to the appearance of clinical symptoms and signs (such as jaundice). Comparable elevations of both AST and ALT are highly characteristic of acute viral, toxic, or nonethanol drug-induced hepatitis. The similar serum transaminase levels in these conditions are thought to be caused by cellular release of only cytoplasmic enzymes associated with reversible hepatic cell damage. In chronic hepatitis and cirrhosis, serum AST levels are higher than ALT; this may reflect hepatic cell necrosis with release of mitochondrial AST. In alcohol hepatitis, AST is more significantly increased than ALT.

Cholestatic lesions associated with either intrahepatic or posthepatic diseases are manifested by modest transaminase elevations, with AST usually exceeding ALT. In these conditions, elevations of serum alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT) are more dramatic.

Since aminotransaminases are ubiquitous in their cellular distribution, serum elevations may occur with a variety of nonhepatobiliary disorders. However, elevations exceeding 10 to 20 times the reference are uncommon in the absence of hepatic cell injury. Since the concentration of ALT is significantly less than AST in all cells except hepatic cytosol, ALT serum elevations are less common in nonhepatic disorders. Following myocardial infarction, AST activity is consistently increased; ALT is associated with passive congestion of the liver. AST and only occasionally ALT serum activity increase in inflammatory skeletal muscle diseases and progressive muscular distrophy.

Measurement of serum ALT activity is routinely used to screen blood donors at risk of transmitting hepatitis, particularly the non-A, non-B type, since no specific serologic test is available. Use of ALT as a surrogate test for non-A,



non-B hepatitis expectedly reduces the incidence of post-transfusion hepatitis by 29%.

References

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